Tuberculosis in the era of TNF-alpha inhibition

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Tuberculosis (TB)

- One-third of world is infected
- In 90%, infection remains latent
- Infection spread limited by immune system
  - Granuloma formation around bacilli
  - Intracellular killing of bacilli
- 10% develop disease
  - Immunosuppression increases risk of progression to disease

Tumor Necrosis Factor–alpha (TNF-α)

- Proinflammatory cytokine
- Expressed primarily by activated Macrophages
  - Also T and B lymphocytes
- Soluble and transmembrane forms
- Biological effects are numerous
  - Sepsis and systemic inflammation
  - Macrophage recruitment and activation
  - Granuloma formation and maintenance

TNF-α Effects

- P55 receptor
  - Primarily binds soluble TNF-α
  - Integral to granuloma formation and maintenance
- P75 receptor
  - Primarily binds transmembrane TNF-α
  - Less important to granuloma formation

TNF-α and TB Infection

- *In vitro*
  - Increases macrophage phagocytosis and killing of *M. tuberculosis* bacilli
  - Induces apoptosis of ineffective macrophages
- *In vivo*
  - Mice deficient in TNF-α / p-55 signaling pathway fail to form granulomas
  - Increased dissemination of TB bacilli
  - Mouse death

Overexpression of TNF-α

- Inflammation and tissue destruction
- Important in pathogenesis
  - Crohn's, rheumatoid arthritis, psoriasis, ankylosing spondylitis, others
- Inhibition of TNF-α highly successful in treatment of these conditions
  - Infliximab, adalimumab (monoclonal antibodies)
  - Etanercept (soluble p75 receptor)

TNF-α Antagonist Therapy

- Often used in combination with methotrexate and/or prednisone
- Many patients have co-morbidities
  - Chronic lung disease, diabetes
- Off-label use frequent
  - Wegener's granulomatosis, uveitis, Bechet's, dermatomyositis, polymyositis, sarcoidosis, giant cell arteritis, others

TNF-α Antagonist Therapy

- Infectious complications
  - TB reported with all 3 drugs
  - Other infections include: histoplasmosis, aspergillosis, candidiasis, listeriosis, others
- U.S. Food and Drug Administration (FDA) adverse event database
  - Collects voluntary reports from physicians

TNF-α Antagonist Therapy and TB

- First published review: Keane *et al, NEJM* 2001
- 70 cases of TB with infliximab
- Atypical clinical presentation
  - —40 (57%) extrapulmonary
  - —17 (24%) disseminated
- Median time to onset, 12 weeks (range,1 to 52 weeks)

Etanercept and TB

- Mohan *et al, CID* 2004
- 25 cases of TB with etanercept
- Atypical presentation
  - 13 (52%) extrapulmonary
  - 3 (12%) disseminated
- Median time to onset, 11.5 months (range, 1-20 months)

TNF-α Antagonist Therapy and TB

- Most recent review: Wallis *et al, CID* 2004 (*Erratum*)
- World-wide TB reports through September 2002
  - 335 infliximab
  - 39 etanercept
- U.S. TB reports over 4 years of study
  - 106 infliximab (rate 54/100,000 treatment starts)
  - 32 etanercept (rate 28/100,000 treatment starts)

Other Reported Infections

- Most are more numerous with infliximab

	Infliximab	Etanercept
Histoplasmosis	39	3
Nontuberculous mycobacteria	31	7
Listeriosis	36	2
Coccidiomycosis	11	1
Candidiasis	38	8
Aspergillosis	29	10
Nocardiosis	10	1

More TB Risk with Infliximab?

- Infliximab drug mechanism differs
- Greater TNF-α binding
  - Transmembrane and soluble TNF-α
  - Forms stable complex
- Longer half-life
- Apoptosis of monocytes and T lymphocytes
- Downregulates interferon-gamma

Interferon-γ Story

- Saliu et al. compared monoclonal antibodies and etanercept
- *In vitro* whole blood culture exposed to TB culture-filtrate or mitogen
  - Exposed to anti-TNF drugs in concentrations typical of trough and peak in body
  - Also, a supratherapeutic etanercept concentration
- Measured t-cell responses, TB growth, cytokine production, apoptosis

Interferon-γ Downregulation

- Adalimumab and infliximab similar
  - Suppressed TB antigen induced INF-γ production (5 days incubation)
  - Decreased T-cell activation (24 hrs incubation)
- No significant difference in TB culture growth at 24 and 96 hours
  - Bacilli grow slowly (doubling time = 15-24 hrs)
- No monocyte or T cell apoptosis seen with any drug

More TB Risk with Infliximab?

- Possible difference in underlying populations receiving the 2 drugs
  - Medical and TB risk factors
  - Use of concomitant methotrexate or corticosteroids
- Limitations of FDA database
  - Under-reporting of cases
  - Cannot rule out reporting bias

UK Biologic Registry

- **9000 patients, followed Dec 2001-Sept 2005.**
- **Physician documented infection**
- **No significant difference between anti-TNF drugs**

	Anti-TNF (n=7,664)	Non-biologic (n=1,354)
RR serious Infection	*1.03 (0.7-1.6)	Ref.
RR skin/soft tissue infection	***4.3 (1.1-17.2)**	Ref.
RR intracellular infection	**Undefined**	Ref

*Adjusted for age, sex, RA severity, extraarticular manifestations, steroids, diabetes, COPD/asthma, smoking

Dixon WG et al. Arthritis and Rheum 2006

Intracellular Infections

- 19 intracellular infections (200/100,000 person-yr)
  - All in anti-TNF treated
  - TB (n=10), NTM (n=1), *Listeria* (n=3), *Salmonella* (n=3), *Legionella* (n=3)
- More TB with monoclonals
  - Infliximab Adj. IRR 4.9 (0.5-49.8)
  - Adalimumab Adj. IRR 3.5 (0.3-47.3)

Emerging Infection Network (EIN) Survey

- Asked for mycobacterial and other infections in last 6 months
- 426 (48.9%) EIN members responded
  - 1876 mycobacterial infections reported
- 49 (2.6%) of associated with biologics
  - 32 cases NTM vs. 17 TB
  - *M. avium* complex most common (n=16)

EIN Survey Results

- **Associated biologics**

	INF	ETN	ADA	RTX	ATC	Unspecified
TB (n=17)	7	4	1	3	0	2
NTM (n=32)	11	8	2	5	0	6

- **21 (42%) patients with concurrent prednisone/MTX**
- **8 (16%) patients died**
- **Other biologic associated infections reported**
  - **Invasive *S. aureus* (n=73) and histoplasmosis (N=56).**

Need for LTBI Screening

- CDC published Morbidity and Mortality Weekly Report (2004)
  - 12 cases in California
  - Most associated with infliximab
  - Many had not been screened for TB
- CDC/FDA editorial in *Arthritis and Rheumatism* (2005)
  - Issued interim TB screening and treatment recommendations

Screening for Latent TB Infection (LTBI)

- Screen BEFORE patient is immunocompromised
- History for TB risk factors
  - Foreign-birth or extended living abroad
  - Previous contact to TB case
  - Previous LTBI diagnosis or treatment
  - Incarceration, homelessness, IV drug use

Screening for Latent TB Infection (LTBI)

- Perform tuberculin skin test (TST)
- Chest radiograph
  - If TST result positive
  - If clinical or epidemiologic suspicion
- Interferon-gamma (INF-γ) release assay (IGRA) testing

IGRAs

- QuantiFERON-TB Gold® test (Cellestis, Australia)
  - Detects cell-mediated immunity
  - Whole blood incubated with TB antigens
  - INF-γ released from sensitized lymphocytes
- T-SPOT.TB ® assay (Oxford, UK)
  - Similar to QFT
  - Measures number of reactive lymphocytes

IGRAs

- Greater specificity for TB than TST
  - No cross reaction with BCG or most NTM
- Little experience screening immunocompromised patients
  - Relative sensitivity unclear
  - Few studies in renal dialysis and Hem/Onc suggest improved sensitivity
  - Several case series in anti-TNF patients suggests similar or better
    - Rheum patients (N=126, anti-TNF or DMARD treated) IGRA more closely associated with LTBI risk factors*
    - 6% indeterminate

*Matulis G et al *Ann Rheum Dis* 2007

LTBI Diagnosis and Treatment

- If anti-TNF drug candidate
  - 5 mm cut-point to define TST positive
  - If TST negative, consider epidemiologic risk factors and radiologic findings
  - Europeans using IGRAs
- Begin LTBI treatment BEFORE starting anti-TNF therapy
  - 9 months isoniazid (INH) preferred in U.S.
  - 4 months rifampin alternative

Recommendation Nuances

- Similar to HIV-infected TB screening guidelines
- No role for anergy panel testing
- Routine “two-step” testing not recommended
  - Specificity issue in countries with high BCG prevalence
- Repeat screening?
  - Did not address
  - Repeat if potential exposure

Evidence Supporting TB Screening

- 83% reduction in infliximab-associated cases Spain *(Carmona et al. Arthritis Rheum 2005)*
  - Use two-step TST
  - 9 months INH
- 85% reduction in adalimumab-associated cases North America/Europe *(Perez et al. EULAR 2005)*
  - Adalimumab dose reduction
  - Use TST and INH similar to CDC recommendations

Why We Left the Motherland

- British Thoracic Society with different view
- Chest radiograph for all
- Do not recommend routine TST
  - Immunosuppressed and too many false negatives
  - Empiric INH in black Africans > 15yo and foreign-born South Asians
- If not immunosuppressed, test with TST
  - Positive ≥ 15mm (if history of BCG)
  - Positive ≥ 5mm in all others

INH Hepatotoxicity

- Hanta et al, *Clin Rheumatol* 2007
  - 5/60 with 3 fold LFT rise
  - No clinical sequelae, all normalized with INH stop
- Baseline and periodic LFT evaluation recommended in these patients

Patients Receiving TNF-α Antagonists

- Physicians should maintain high index of suspicion for TB disease
  - —Febrile or respiratory illness
- If TB diagnosed
  - – Begin anti-TB treatment
- Stop anti-TNF therapy immediately?
  - – Immune reconstitution inflammatory syndrome (IRIS), although rare in EIN study
  - – Unclear when to re-start anti-TNF therapy

Use of Immunosuppressing Drugs During Treatment of TB Disease

- Corticosteroids
  - —Used in meningeal and pericardial TB
- Azathioprine and cyclosporine
  - —Used safely in organ recipients with TB
- Anti-T-cell antibodies
  - —Organ recipients with TB have worsened outcome
  - – Due to worsened organ function vs. interaction with TB therapy

Anti-TNF Drugs During Treatment of TB Disease

- Little data available
- Recent small study (n=16) HIV-infected TB patients
  - Concurrent therapy with etanercept was safe
  - Trend toward improved TB outcome
    - Historical control group used
    - Limited power
    - Clinical significance unclear

Needed Research

- Utility of INF-γ release assays in screening anti-TNF candidates for LTBI
- Clinical studies to assess effect of anti-TNF drugs on LTBI and TB treatment
  - Improved or worsened outcome?
  - Duration of TB treatment?
- Studies to assess the infectious risk of different biologics and combination therapy
  - Biologic, methotrexate, and corticosteroid

Next Steps

- Convene experts and public health agencies (ATS/IDSA/CDC)
  - Review and propose research
  - Further refine and issue U.S. screening and treatment guidelines

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Prednisone and Tuberculosis

- Risk of reactivation TB poorly defined
  - Based on anecdotal reports from 1950-70s
- CDC 2000 TB statement
  - ≥15mg/day for one month or more
  - Dose shown to suppress tuberculin skin test reactivity
- No observational or prospective data to support
- Retrospective studies in low incidence areas unable to demonstrate any risk of TB

Finally Some Data

- ***Jick et al. Arthritis Rheum 2006***
- **General Practice Research Database, UK**
- **TB cases 1990-2001 and controls†**
- **Current glucocorticoid use *OR 4.9 (2.9-8.3)**
- **≤15mg/day *OR 2.8 (1.0-7.9)**
- **≥15mg/day *OR 7.7 (2.8-21.4)**
  - **Causal versus severity of underlying disease**

*Adjusted for smoking, BMI, lung disease, diabetes, anti-rheumatic therapy, other TB risk factors

†Controls matched for age, sex, residence, time clinically followed

Case Report

- 64-year old woman with rheumatoid arthritis
- Began infliximab (September 2001)
- After seven doses, fever and weight loss (April 2002)
- Chest radiograph with pericardial effusion and a right-upper lobe infiltrate
- Pericardial and pulmonary multi-drug resistant TB diagnosed

Case Report

- Physician unaware of TB risk before starting infliximab
- Patient born in Philippines
- Patient had contact to pan-sensitive TB case in 1999
- Negative tuberculin skin test (TST) in 2000
  - But on prednisone at time of TST

INH Hepatotoxicity

- Prospective study: Nolan *et al, JAMA* 1999
  - 11,141 consecutive patients in Seattle, WA
  - 0.10% to 0.15% developed clinically significant hepatitis
  - Median onset 9 weeks (range, 3-22 weeks)
  - No data on underlying liver disease or use of other drugs

Rheumatoid Arthritis and Prednisone

- Current usage is prevalent
  - 47% in Doran study (pre-year 2000)
  - 35% in recent survey in US (2004, in press)
    - Use increases with severity of RA
    - Decreases with start of TNF blockade
- Infection risk with prednisone well-described, but not well-quantified
  - Tuberculosis, other opportunistic infections, routine bacterial pathogens

Adalimumab and TB

- Commercially available for less time than other drugs
  - FDA approval August 2004
- Clinical trials North America and Europe
  - 34 cases TB in 14,544 patient years of exposure
  - (234 cases/100,000 patient-years)

Key References

- American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-247.
- CDC: Guidelines for using the QuantiFERON®-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. MMWR 2003; 52(RR02):15-18.
- CDC: Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection---United States, 2003. MMWR 2003;52(31):735-739.
- Mohan AK, Cote TR, Siegel JN, Braun MM. Infectious complications of biologic treatments of Rheumatoid Arthritis. Curr Opinion Rheumatol 2003; 15:179-84.
- Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of Etanercept: a tumor necrosis factor inhibitor. Clin Infect Dis 2004:39:295-299.

Key References

- Blumberg HM, Burman WJ, Chaisson RE, et al. Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-662.
- Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor-α neutralizing agent. NEJM 2001;345:1098-1104.
- Nolan C, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7 year survey from a public health tuberculosis clinic. JAMA 1999;281:1014-1018.
- Wallis RS, Broder MS, Wong JY, Hanson ME, Breenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261-1265.
- Wallis RS. Granulomatous infectious diseases associated with tumor necrosis factor antagonists [*Erratum*] *(*In Press, Clin Infect Dis)

Key References

- Wallis RS, Kyambadde P, Johnson JL, et al. A study of the safety, immunology, virology, and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. AIDS 2004;18:257-264.